

Nitrates in the Treatment of Angina and Heart Failure

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Organic nitrates include drugs such as nitroglycerin, isosorbide mononitrate, and isosorbide dinitrate. A newer organic nitrate that has recently been evaluated is pentaerythritol tetranitrate. Nitrates are available in various forms: intravenous, oral, sublingual, spray, ointment, patch, transdermal, and buccal preparations.



Heart Failure and Angina

The **ventricle** is the chamber of the heart that is responsible for the pumping of blood throughout the body. Heart failure results when the ability of the ventricles to fill and pump the **blood** outside the **heart** is impaired. Heart failure may be due to a **change in the structural and functional feature of the ventricle.**

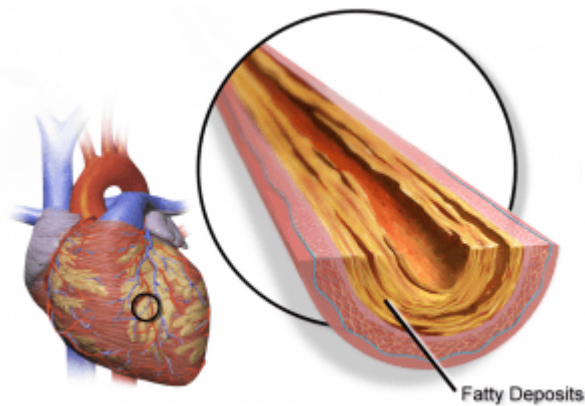


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Heart failure is classified as either **reduced or preserved ejection fraction heart failure** based on the left ventricular ejection fraction. It can also be classified as **chronic or acute heart failure** and **decompensated or non-decompensated heart failure**. In most cases, both of those terminologies are combined. Treatment of heart failure is greatly dependent upon understanding these classifications.

Angina is a state in which blood supply to parts of the heart is compromised and, with progression, can lead to the development of **myocardial infarction** (irreversible death of the heart muscle). The nitrates form a group of drugs that are helpful and essential in the treatment of both angina and heart failure.

Nitrates in the Treatment of Angina and Heart Failure

Functional mechanism of action – anti-anginal effect

Nitrates work by causing **systemic vasodilation**, predominantly **venodilation**. The venodilation reduces the preload to the heart. In addition, they also cause **coronary vasodilation**, which increases the blood supply to the parts of the heart experiencing an [ischemic attack](#). The large coronary arteries are dilated, which benefits the ischemic zone the most.

Nitrates have an effect on the afterload of the heart, especially when administered at higher doses. A **decrease in the afterload** results, which thereby decreases the stress on the heart as it pumps against resistance. Thus, nitrates target the three important stressors to the ischemic heart: preload, afterload, and decrease in the blood supply to the area.

Coronary collateral vessels are normally formed in a case of compromised blood supply to any region of the heart. Nitrates **enhance blood flow in the collateral circulation**. They also have **antiplatelet and antithrombotic properties** (stimulation of **guanylyl cyclase** in platelets, inhibiting the binding of fibrinogen to the platelet IIb and IIIa receptors).

Functional mechanism of action – treatment of heart

failure

The main mechanism of action for nitrates in the treatment of heart failure is **venous and arterial dilation**. This dilation decreases the preload and afterload to the heart, as discussed earlier.

Biochemical mechanism of action

Nitrates are **converted to nitric oxide** after entering the cell. This conversion occurs in two possible ways. In high potency nitrates (**nitroglycerin and nitroprusside**), the conversion is caused by the **mitochondrial aldehyde dehydrogenase 2 (ALDH2) enzyme** and, in low potency nitrates (**isosorbide dinitrate and isosorbide mononitrate**), the conversion occurs with the help of **endoplasmic reticulum P450**. The nitric oxide then attaches to the **sulfhydryl group**, forming the **S-nitrosothiols**. S-nitrosothiols stimulate **guanylyl cyclase enzyme**.

Guanylyl cyclase is responsible for the conversion of **guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP)**, which facilitates **dilation of the smooth muscle of the blood vessels**. Since smooth muscle is present in both arteries and veins, nitrates successfully dilate both.

Pros & cons and the main indication of nitrates

Angina

Sublingual nitroglycerin is the drug of choice **to treat acute anginal episodes**. The dose administered is **0.4 mg every 5 minutes**; a maximum of 3 doses can be given to the patient. In the case of **heart pain**, self-administration of nitroglycerin is recommended, but emergency medical services (EMS) needs to be called if the pain does not subside after a single dose. Nitroglycerin is also used as **prophylactic therapy** for patients before they undertake a maneuver that may precipitate angina (the evidence to support this varies). A patient whose condition has not resolved after 3 doses is a potential candidate for **intravenous nitroglycerin**.

The intravenous nitroglycerin is given at a **starting infusion rate of 5 to 10 µg/min**. The main goal is to relieve the patient's symptoms of angina pain. Caution must be exercised to ensure the systolic blood pressure does not decrease more than 90 mmHg. After 48 hours of treatment, the oral and topical forms of nitroglycerin therapy can be used.

Acute coronary syndrome (unstable angina)

Similar to the treatment of angina, sublingual nitroglycerin, followed by intravenous nitroglycerin (in a patient whose symptoms have not resolved), is given. The cornerstone lies in treating the patient with a **regimen of beta blockers, nitrates, antithrombotic, and antiplatelet therapy** (after assessing the cause). Nitrates also help reduce **coronary vasospasm**.

Chronic stable angina

The difference between nitroglycerin and isosorbide dinitrate pharmacokinetically is that nitroglycerin has a shorter onset of action (2-3 min), compared to isosorbide dinitrate, which has an onset of action of 15 to 30 minutes. The duration of action also varies between both the drugs (15-30 min for nitroglycerin and 3-6 hours in the case of

isosorbide dinitrate). As a result of this difference, **isosorbide dinitrate** is mainly used for the treatment of chronic stable angina.

Acute myocardial infarction

Nitrates do not offer any survival benefit in the case of myocardial infarction. They are mostly contraindicated in patients with hypotension. Also, beta blockers, which offer a survival advantage, are the preferred treatment over nitrates. The administration of nitrates should not preclude the use of the beta blockers. Reperfusion therapy is the main treatment of acute myocardial infarction (this includes direct percutaneous intervention and thrombolytic therapy).

Variant (Prinzmetal angina)

Coronary vasoconstriction is responsible for ischemic pain with variant angina. A **calcium channel blocker** has shown to be more efficacious for this condition when compared to the use of nitrates. Nitrates, when given, are administered with a calcium channel blocker.

Heart failure

Nitrates are not recommended for the treatment of patients with heart failure with preserved ejection fraction. In a recent trial of 110 patients, where the effect of isosorbide mononitrate was compared to that of a placebo, it was found that the use of isosorbide mononitrate decreases the daily activity level of the patient with preserved ejection fraction heart failure. The main indication for the use of nitrates is to treat acute decompensated heart failure, especially in patients with an increase in blood pressure.

Acute decompensated heart failure (ADHF)

The initial therapy for acute decompensated heart failure consists of **ventilation** (for respiratory distress) and use of a **loop diuretic** (for fluid overload). Nitrates are especially indicated in patients with heart failure and elevated blood pressure. The intravenous dose of nitroglycerin in patients with ADHF includes a **starting dose of 5 to 10 µg/min**, with incremental increases in the dose every 5 minutes, at a rate of 5 µg/min.

Nitroprusside, which is more potent than nitroglycerin, requires continuous hemodynamic monitoring in the form of an intra-arterial catheter. Isosorbide dinitrate can also be used for the treatment of ADHF, but it is not the treatment of choice because it has a long half-life (it will be difficult to correct when hypotension occurs in the treatment).

Different Preparation and their Usefulness in the Treatment of Angina and Heart Failure

The transdermal nitroglycerin patch gained popularity mainly due to the **ease of administration**. The patch consists of a semi-permeable membrane that separates the reservoir of drug and the skin.

Adverse and Side Effects Related to Nitrates

Since nitrates cause systemic vasodilation, one of the expected adverse effects is **hypotension**. This can be corrected by **volume infusion**. In addition, the patient may

experience **headache, tachycardia** (an increase in the heart rate, which occurs as a compensatory mechanism when a decrease in blood pressure occurs), and **flushing**.

Nitrates, when infused for a longer period, can cause **methemoglobinemia**. In this condition, methemoglobin forms in the red blood cells. Methemoglobin contains the ferric form of iron in the core and has a decreased affinity for oxygen binding. Nitrates cause oxidation of the ferrous ions to ferric ions. At the same time, it hinders the release of the oxygen from other ferrous ions. Thus, the ability to attach, as well as release, is impaired, causing the oxygen-hemoglobin dissociation curve to shift to the left. The tissue undergoes **hypoxia**, and the **blood changes from a red color to a bluish color**. The treatment for this condition is **intravenous methylene blue**. It hastens the conversion of methemoglobin to hemoglobin.

Contraindication of Nitroglycerin

The administration of nitrates to a patient who is hypotensive (systolic blood pressure less than 90 mm Hg) is contraindicated, as it might further aggravate the hypotension. The patient with an **increased risk of decompensation**, as noted by the occurrence of **bradycardia or tachycardia**, is not a candidate for treatment with nitrates.

A patient who has taken **drugs to treat erectile dysfunction** (sildenafil, tadalafil, and vardenafil) should not be prescribed nitrates. These drugs are phosphodiesterase-5 inhibitors, and their mechanism of action increases the concentration of cGMP by preventing its breakdown, thereby causing dilation of the blood vessel. Cumulative **hypotension**, which can be life-threatening, can occur as a result.

There is already **compromised output from the heart** in patients with **hypertrophic cardiomyopathy** and **severe aortic stenosis**, so the administration of nitrates leads to a compromised ejection fraction of the heart. In patients who have a **massive right ventricular infarction**, the risk of **hypertension** increases with the use of nitrates. Nitroprusside can cause **cyanide toxicity**. Nitroprusside normally metabolizes into cyanide, and the cyanide is detoxified by the conversion into thiocyanate, which occurs in the **liver** and kidney. Patients who are on **long-term treatment with nitroprusside** run the **risk of cyanide accumulation in the blood**.

Nitrate Tolerance

Nitrate tolerance may result in the **loss of the therapeutic benefit** of a decrease in blood pressure after drug administration. This occurs in many patients **after 24 hours of therapy**.

The mechanism behind the nitrate tolerance can be divided into early and late causes. The **compensatory neurohormonal activation** of the body is the initial mechanism for the loss of effect seen with nitrates. In the long term, the decrease in the biotransformation of the nitrates by the inhibition of the ALDH2 is a proposed reason. The inhibition of this enzyme is caused by the stimulation of **vascular superoxide and peroxynitrite formation** by nitrates. One of the other reasons proposed is the **nitrate-induced endothelial dysfunction**, which occurs in the treatment.

Since intravenous nitroglycerin forms part of the initial emergency therapy for patients with angina and is not given in the long term, the tolerance can be overlooked in many cases. But, in the case of isosorbide dinitrate and isosorbide mononitrate, which are given long term for the treatment of chronic stable angina, tolerance is an important concern.

The **nitrate-free interval** in between the treatment with nitrates is a proposed solution to the problem. However, it increases the **risk of rebound angina**.

Newer Drug for Angina and Heart Failure

Pentaerythritol tetranitrate is a drug mainly investigated for its possible effectiveness without the development of nitrate tolerance. But in a recent randomized, multicenter trial, which compared pentaerythritol tetranitrate to placebo in patients with chronic stable angina, the drug was **no more effective** when compared to the placebo.

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